Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 58422

Title: Noninvasive markers of liver steatosis and fibrosis after liver transplantation - Where do we stand?

Reviewer's code: 00723680
Position: Peer Reviewer
Academic degree: MD
Professional title: Attending Doctor
Reviewer's Country/Territory: Taiwan
Author's Country/Territory: Croatia

Manuscript submission date: 2020-07-21
Reviewer chosen by: AI Technique
Reviewer accepted review: 2020-07-26 00:00
Reviewer performed review: 2020-08-02 06:23
Review time: 7 Days and 6 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

SPECIFIC COMMENTS TO AUTHORS

1. This review article summarized clinical tools that are currently available for assessment of graft steatosis and fibrosis after liver transplantation. These tools included various laboratory markers and imaging modalities, mainly ultrasound-based technology. 2. The article spent more spaces in discussing the background of steatosis than fibrosis. This created a sense of imbalance, since steatosis and fibrosis were both stated in the title. Whether the word "fibrosis" specifically referred to "fibrosis related to NAFLD" need to be clarified. If not, it seems that the article omitted substantial contents regarding graft fibrosis. 3. The first three paragraphs of TRANSIENT ELASTOGRAPHY mentioned the utility of TE and CAP for assessment of NAFLD in the pre-LT status, which is not the main focus of this article (post-LT). It is probably better try to reduce the length of this section and make it more concise for the readers. 4. pSWE/SWE are widely utilized in current practice. MR elastography is also an emerging imaging modality. The article only mentioned these tools briefly, which is probably inadequate to provide a general picture for the readers interested in this field. 5. MRI is also capable of assessing liver steatosis using different kinds of methods, and are currently available for clinical application. 6. In the third paragraph of “Usefulness of transient elastography in the post-LT setting” - “…..TE with CAP in diagnosing fatty liver disease in nontransplant patients.”: nontransplant ? 7. In the last sentence of the last paragraph of “Usefulness of transient elastography in the post-LT setting” - “Until then, imaging methods could identify NAFL, but LB should be used to identify NASH [16].”: NAFL ?

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 58422

Title: Noninvasive markers of liver steatosis and fibrosis after liver transplantation - Where do we stand?

Reviewer's code: 03668558
Position: Editorial Board
Academic degree: MD

Professional title: Consultant Physician-Scientist, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Croatia

Manuscript submission date: 2020-07-21

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2020-09-28 06:12

Reviewer performed review: 2020-09-28 08:19

Review time: 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

SPECIFIC COMMENTS TO AUTHORS

This review by Dr. Mikolasevic and collaborators focused on steatosis and fibrosis after liver transplantation. The topic is of interest, given the high prevalence of both conditions after transplantation, and the significant improvement of patient outcomes after introduction of specific treatments for viral hepatitis. My comments: - The Authors cited a study by Baghat et al (ref #11) saying that recurrent steatosis and steatohepatitis were more frequent after LT in patients with NASH than in those with alcoholic liver disease. The latter group may experience a de novo steatohepatitis, and not a recurrent. - A high rate of BPAR is not a common finding in patients with NAFLD. - I suggest to use the term NAFLD more frequently, replacing, whenever possible, the term NASH (i.e., transplant for NAFLD instead of "transplant for NASH"), in order to make the manuscript easy to understand. Similarly, the term NAFL appears only at page 19, whereas steatosis is adopted throughout the manuscript. - In my opinion, the section "Nonalcoholic Fatty Liver Disease After Liver Transplantation" should be re-considered, highlighting results provided by cited metanalysis and summarizing current gaps of knowledge on NAFLD (both de novo and recurrent) after LT. For instance, prevalence of post-LT NAFLD differed across studies also because of different follow-up time, different diagnostic tools used, etc.. - The Authors said that non-invasive tools as APRI, FIB-4, NFS are not so useful in the post-LT setting due intrinsic pitfalls (i.e., thrombocytopenia). Nevertheless, they cited many studies which demonstrated a good accuracy also in the post-LT setting. A further interpretation given by the Authors may be important for the Readers on this issue. - The Authors well described potential pitfalls of Transient elastography for a non-invasive assessment of fibrosis. Nevertheless, they mentioned studies on pre-LT setting. I suggest to focus more on post-LT patients, shortening the first paragraph. Moreover, the usefulness of TE for ACR or during donor

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

graft evaluation is interesting, but in my opinion goes beyond the scope of this manuscript. - I agree with the Authors that no drugs are currently available for the management of NAFLD, especially in the post-LT setting. Nevertheless, monitoring NAFLD may be useful also in the setting of immunosuppression management. - English language polishing needed. There are some redundant sentences that would be shortened or deleted. Minor: - ref#11: Baghat instead of Baghet - per protocol instead of protocolary - page 18: post-transplant instead of non-transplant ? - Ref # 76: the follow-up time should be mentioned, in order to better understand the high prevalence of post-LT cirrhosis

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 58422

Title: Noninvasive markers of liver steatosis and fibrosis after liver transplantation - Where do we stand?

Reviewer's code: 02537773
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Academic Research, Associate Professor, Doctor, Lecturer
Reviewer's Country/Territory: Germany
Author's Country/Territory: Croatia

Manuscript submission date: 2020-07-21
Reviewer chosen by: Ya-Juan Ma
Reviewer accepted review: 2020-09-24 11:41
Reviewer performed review: 2020-10-03 16:46
Review time: 9 Days and 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

SPECIFIC COMMENTS TO AUTHORS

In the invited review the authors aimed to summarize the data on evaluation of steatosis and fibrosis after liver transplant settings in particular in the context of recurrent NAFLD. Overall, the review is well written although it is quite lengthy and has only two tables, no figures, which are, to my view, necessary to attract the readership. The review has multiple parts that can be probably better structured to allow the reader better orientation. Having the main focus on non-invasive markers of liver steatosis and fibrosis after liver transplantation, almost 5 pages are related to overall Non-alcoholic fatty liver disease after LT. While the information is important it may be important to include a figure or at least table to summarize the lengthy content. The key message is to provide the global overview on existing methods to evaluate fibrosis and steatosis in post LT subjects. Surprisingly, the TE and CAP (Fibroscan) receive the largest attention while SWE and MRI elastography receive very little attention. Since the focus is set to global non-invasive methods and markers, it is recommended to expand on this topic. Alternatively, the title needs to be adjusted to the transient elastography. It is also important to expand on the point that identification of NAFLD in post LT settings does not mean to have therapeutic options and it is quite questionable to reflect on economic burden and potential consequences. No doubt that biochemical markers including APRI and Fib4 are and will be useless in such a complex condition as post LT. A clear statement in the related chapter may be helpful. I would recommend revising the sentence:. “It has been suggested that LB is the best available standard of reference for fibrosis evaluation, although it is an imperfect gold standard because we do not have a better reference standard”. At present it is well accepted that histology is the gold standard (it is not suggested), the second part of the sentence makes no sense. Besides, histology provides also additional information regarding the other common

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

questions including rejection etc. Separating chapter on CAP may be recommended to allow better structuring of the paper. The authors state the potential of CAP to replace the liver biopsy for assessment of liver fat assessment. Unfortunately, at present it is not sufficient evidence to support this message. While TE (including SWE) indeed helps the evaluation of fibrosis, the CAP values are still very heterogeneous and it is too early to state the value of CAP in post liver transplant. One of the most significant limitations so CAP is the missing outcome based on the CAP-values. Page 18: sentence needs revision- "...ill defined". Please consider revising similar sentences.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Transplantation

Manuscript NO: 58422

Title: Noninvasive markers of liver steatosis and fibrosis after liver transplantation - Where do we stand?

Reviewer's code: 03668558
Position: Editorial Board
Academic degree: MD

Professional title: Consultant Physician-Scientist, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Croatia

Manuscript submission date: 2020-07-21

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-12-11 16:26

Reviewer performed review: 2020-12-13 08:26

Review time: 1 Day and 16 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

In my opinion, the paper underwent minor improvements after revision. In detail, as previously mentioned, there are still many paragraphs which describes pathogenetic mechanisms, as well as diagnostic tools, in a setting which is different from that expected from the Title. - The section entitled "The usefulness of biochemical markers after liver transplantation" describes many studies which focused on patients with hepatitis C (see page 9), but this was not the scope of this manuscript. - The sections entitled "Ultrasound" and "Effects of probe choice on transient elastography results" describe the effectiveness of US for diagnosis of steatosis, in the non-transplant setting (see page 12). Furthermore, I previously suggested to shorten several sections (as the part dealing with the use of TE for diagnosis of ACR). It remains difficult to understand if the terms NAFL, NAFLD, NASH are used as synonyms or not throughout the manuscript. Regarding minor comments raised before, I do not find the follow-up time regarding ref#76 in the revised manuscript (as requested before), and the term "protocolary" appear also in this version.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Transplantation

Manuscript NO: 58422

Title: Noninvasive markers of liver steatosis and fibrosis after liver transplantation - Where do we stand?

Reviewer's code: 02537773
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Academic Research, Associate Professor, Doctor, Lecturer
Reviewer's Country/Territory: Germany
Author's Country/Territory: Croatia
Manuscript submission date: 2020-07-21
Reviewer chosen by: Le Zhang
Reviewer accepted review: 2020-12-13 12:32
Reviewer performed review: 2020-12-13 13:11
Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Unfortunately, quite unacceptable point-by-point response to the comments of reviewers. The track-change version is also not included. The value of CAP in hepatology is partially controversial and not sufficiently supported by the hard scientific evidence and outcomes (as partially discussed in the review). It should be the focus of the research and hard statements and recommendation may be out of the scientific value/evidence. This is relevant not only to the NAFLD, but also even more for the post LTX NAFLD subjects. As far the reviewer can identify the changes, certain parts of the paper have been expended and tables included. Some issues not addressed. The quality may be acceptable.